IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Frank H. Portugal, *et al.*	§	Examiner: J. Souaya
	§	Group Art Unit: 1655
Serial No.: 09/027,439	§	Attorney Docket No.: 044198.0000
Filed: February 20, 1998	§	
For: Compositions and Methods for Differentiating Among *Shigella*-Species and *Shigella* from *E. Coli* Species	§	

CERTIFICATE OF MAILING
37 C.F.R. §1.8
I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231, on the date below:

August 4, 2000 (Date) — Gloria L. Norberg (Gloria L. Norberg)

Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR EXTENSION OF TIME; AMENDMENT; AND RESPONSE TO OFFICE ACTION MAILED APRIL 4, 2000

Sir:

The present paper is submitted as a complete response to the Official Action mailed April 4, 2000. The present paper is timely filed, as the present paper is also a request for an extension of time of one month to and including August 4, 2000. Should any further extension of time be required, this document is such a request. Enclosed is a check in the amount of $94.00 for the fee for a one-month extension of time and for one additional independent claim. Should any further fees be due with the filing of the present document, or should an overpayment be included therein, the Commissioner is authorized to deduct or credit said fees from Akin, Gump, Strauss, Hauer & Feld, L.L.P. Deposit Account No. 01-0660.

AMENDMENT

In the Claims:

08/15/2000 AWONDAF1 00000049 09027439
01 FC:215 55.00 OP
02 FC:202 39.00 OP

Please cancel Claims 1-20.

Please add Claims 37-44 as follows.

--37. A purified nucleic acid molecule of 10 to 40 nucleotides for distinguishing *E. coli* from Shigella species, the molecule comprising: a sequence of nucleotides from SEQ ID NO:7 and comprising an identifying inserted nucleotide U or T in between positions 88 and 89 of 16s ribosomal RNA or 16 s ribosomal DNA, respectively, with position reference to an *E. coli* equivalent position of SEQ ID NO:7, the identifying nucleotide presence indicating *E. coli* species and distinguishing *E. coli* from Shigella species, or a nucleic acid molecule complementary to said molecule.

38. A purified nucleic acid molecule of 10 to 40 nucleotides for identifying *Shigella sonnei* species, the molecule comprising: a sequence of nucleotides from Table 2 and comprising an identifying nucleotide C at position 964 or a deletion at position 978 with resulting frameshift of 16s ribosomal RNA or 16 s ribosomal DNA, with position reference to an *E. coli* equivalent position of SEQ ID NO:7, the identifying nucleotide presence or the deletion indicating *Shigella sonnei* species and distinguishing from *E. coli* and from other Shigella species, or a nucleic acid molecule complementary to said molecule.

39. A purified nucleic acid molecule of 10 to 40 nucleotides for identifying *Shigella dysenteriae* species, the molecule comprising: a sequence of nucleotides from Table 2 and comprising an identifying nucleotide A at position 76 of 16s ribosomal RNA or 16 s ribosomal DNA, with position reference to an *E. coli* equivalent position of SEQ ID NO:7, the identifying nucleotide presence indicating *Shigella dysenteriae* species and distinguishing from *E. coli* and from other Shigella species, or a nucleic acid molecule complementary to said molecule.

40. A purified nucleic acid molecule of 10 to 40 nucleotides for identifying *Shigella dysenteriae* species, the molecule comprising: a sequence of nucleotides from Table 2 and comprising an identifying nucleotide in region 1001-1040 as set forth in Table 2 of 16s ribosomal RNA or 16 s ribosomal DNA, with position reference to an *E. coli* equivalent position of SEQ ID NO:7, the identifying nucleotide presence indicating *Shigella dysenteriae* species and distinguishing from *E. coli* and from other Shigella species, or a nucleic acid molecule complementary to said molecule.

41. A purified nucleic acid molecule of 10 to 40 nucleotides for identifying *Shigella boydii* species, the molecule comprising: a sequence of nucleotides from Table 2 and comprising an identifying nucleotide C at position 92 of 16s ribosomal RNA or 16 s ribosomal DNA, with position reference to an *E. coli* equivalent position of SEQ ID NO:7, the identifying nucleotide presence indicating *Shigella boydii* species and distinguishing from *E. coli* and from other Shigella species, or a nucleic acid molecule complementary to said molecule.

42. A purified nucleic acid molecule having a nucleotide sequence as set forth in SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NO:6, or a nucleic acid complementary to said purified molecule.

43. A purified nucleic acid molecule having a nucleotide sequence as set forth in SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, or SEQ ID NO:20, or a nucleic acid complementary to said purified molecule.

44. A purified nucleic acid molecule having a nucleotide sequence as set forth in SEQ ID NO:21, or a nucleic acid complementary to said purified molecule.--

REMARKS

I. Status of Claims

Claims 1-20 are canceled. Claims 37-44 are added. Claims 37-44 are pending. Claims 20-36 are withdrawn as nonelected.

II. Rejection of Claims 1-19 under 35 U.S.C. § 112, 2nd Paragraph

The Office Action rejected claims 1-19 as indefinite for lacking clarity for the term "identifying nucleotide," lacking clarity for the numbering of each nucleotide position in the sequence of Shigella, or for a believed ambiguity in the term "a nucleic acid complementary" in Claim 19.

Response

The terms used in the claims are defined in the specification. When read in light of the specification, the claims are believed to meet the requirements of 35 U.S.C. § 112, 2nd paragraph, for the following reasons.

"Identifying nucleotide" The term "identifying nucleotide" is defined in the specification on p. 6, lines 6-7:

> "By identifying or distinguishing nucleotide is meant a nucleotide that differs in kind or in its presence or absence as compared to an *E.coli*-equivalent position."

Note that detection of an identifying nucleotide determines presence of that species, while lack of

detection of a particular identifying nucleotide does not necessarily mean absence of that species, see p 5, line 30- p 6, line 1 of the specification.

Applicant therefore believes that "identifying nucleotide" is clear. "Identifying nucleotide" refers to a polymorphism if that polymorphism is in Table 2.

"Nucleotide Position" The claims recite "with position reference to *E. coli* equivalent position of SEQ ID NO:7." The numbering system used in *Shigella* sequences is based on a comparison of *Shigella* sequences to *E. coli* sequences. Note that the numbering system of Table 2 and "*E. coli*-equivalent position" are defined in the specification on p 6, line 26 to p. 7, lines 2-4:

> "The reference numbering system of Table 2 is the rDNA sequence corresponding to the rRNA sequence of *E. coli* 16 s RNA strain 7 as provided in GenBank as ECORRD, and as provided as SEQ ID NO:7. The sequences of 16s rRNA or rDNA of Shigella species regions are aligned to maximally match the *E. coli* sequence. To maximize alignment, adjustments are made in the Shigella sequence, not the *E.coli* sequence. For example, as herein described, an insertion of a nucleotide into the Shigella sequence as compared to the *E.coli* sequence is designated herein as a "p" nucleotide. A deletion is designated as an "X" nucleotide. "*E.coli*-equivalent position" as used herein, means that such an alignment of *Shigella* sequences has been carried out and an *E.coli* equivalent number has been assigned to a *Shigella* nucleotide position."

The reference numbering used in Table 2 is further explained in footnotes 1 and 2 to Table 2:

> "1 Data for *E. coli* strain 7 are from the GenBank ECORRD Sequence Data Bank for 16s rDNA..."
> "2 The numbering of the region follows the numbering for the *E. coli* sequence ECORRD."

"Nucleic acid complementary" Nucleic acid sequences which are "complementary" are those that are capable of base-pairing according to the standard Watson-Crick complementarity rules. As used in the specification, the term "complementary sequences" means nucleic acid

sequences which are substantially complementary or as defined as being capable of hybridizing to the nucleic acid segment of said sequences under relatively stringent conditions (specification, p 14, lines 9-14). Included within the term "nucleic acid sequence" are sequences that substantially correspond to a portion of the cited sequences, and have few nucleotides that are not identical, or functionally equivalent, to the nucleotides of said sequences. The term "functionally equivalent" is defined at page 13, lines 15-22.

In light of the pending claims and the specification, Applicants submit that the claim language is definite and respectfully request that the rejection under U.S.C. §112 be withdrawn.

III. Rejection of Claims 1-4, 6, 8, 11-13, and 20 under 35 U.S.C. §102(a)

The Office Action rejected Claims 1, 3-4, 6, 8, 11, 13, and 20 as anticipated by Cilia *et al.*(Applicant's reference C1) and accession number X80726. The Office Action states that the accession no. citation teaches a part of the S. sonnei gene for 16s ribosomal DNA.

Claims 2, 12, and 20 were rejected for being anticipated by Cilia *et al.* and accession numbers X80723 and X80724. The Office Action states that accession no. X80723 teaches sequences 71-100 of E. coli rrnC which will distinguish E. coli from Shigella, and that accession no. X80724 teaches nucleotides 71-100 of an E. coli 16s gene which will distinguish E. coli from Shigella.

Response

For a prior art reference to anticipate a claimed invention, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 910 F.2d 831, 14 USPQ.2d 1566-1568 (Fed. Cir. 1990).

Neither Cilia nor the sequences of the accession cites teach the identifying inserted nucleotide U or T in between positions 88 and 89 for distinguishing E. coli from Shigella species (Claim 37), the identifying nucleotide C at position 964 or a deletion with resulting frameshift at position 978 for distinguishing Shigella sonnei (Claim 38), the identifying nucleotide A at position 76 for identifying Shigella dysenteriae (Claim 39), the identifying nucleotide region 1001-1040 as set forth in Table 2 for identifying Shigella dysenteriae (Claim 40), the identifying nucleotide C at position 92 for identifying Shigella boydii (Claim 41), or the nucleic acid molecules having the SEQ ID NOS as set forth in Claims 42-44.

Since these elements of the claims are missing from Cilia and the cited accession sequences, Applicants respectfully request that the rejection under 102(a) be withdrawn.

IV. Common ownership

The Office Action reiterates the 37 CFR 1.56 requirement to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made.

Response

The claimed invention was commonly owned at the time the invention was made.

V. Rejection of Claims 1-18 and 20 under 35 U.S.C. § 103(a)

The Office Action rejected Claims 1-18 and 20 under 35 U.S.C.§ 103(a) over Cilia *et al.* or over Hogan *et al* ('321). in view of Faruque *et al.* (Applicant's reference C2). Cilia is cited as teaching sequence heterogeneities among 16s RNA sequences of *E. coli* and *Shigella*. Hogan is cited as teaching hybridization of E.coli probes to closely related organisms such as Shigella

boydii, Shigella flexneri, Shigella dysentereiae, and Shigella sonnei at column 52, table 54. Faruque is cited as teaching distinguishing *Shigella flexneri* strains by observing the restriction patterns of rRNA genes. The Office Action states that, since the sequences of 16s rRNA and rDNA of Shigella species and E. coli species were known at the time of the invention, it would have been obvious for the ordinary artisan to construct probes and primers to regions of variability to differentiate closely related bacteria.

Response

Non-obviousness is determined by application of both factual inquiries and secondary considerations as set forth by the Supreme Court in *Graham v. John Deere*, 148 USPQ 459 (1966). Factual inquiries include the scope and content of the prior art and the difference between prior art and the claims at issue. Applicants submit that the invention as claimed would not have been obvious to one of ordinary skill in the art at the time the invention was made over Cilia or over Hogan in view of Faruque for the following reasons.

Scope and content of prior art

Cilia teaches an alignment of 16s RNA sequences for certain Enterobacteriaceae and for seven operons of E. coli strain PK3. Alignment is provided for regions 79-93, 249-272 and 1000-1039. Included in the alignment is one sequence from each of Shigella flexneri, Shigella dysenteriae, and Shigella sonnei.

Hogan teaches detection of E.coli using a probe from the region of 995-1030 of 16s rRNA (column 51, lines 42-43).

Faruque teaches differentiation of Shigella flexneri strains by rRNA gene restriction patterns.

Difference between the prior art and the claimed invention

Cilia does not teach or suggest the identifying inserted nucleotide U or T in between positions 88 and 89 for distinguishing E. coli from Shigella species (Claim 37). While a "T" is present at that position in Cilia, Cilia does not recognize that that "T" is a genus-specific nucleotide. Cilia does not teach or suggest the identifying nucleotide C at position 964 or a deletion with resulting frameshift at position 978 for distinguishing Shigella sonnei (Claim 38). In fact, Cilia does not include the region having these nucleotides in the alignment figure. Cilia does not teach or suggest the identifying nucleotide A at position 76 for identifying Shigella dysenteriae (Claim 39) since that region falls outside of the alignment of Cilia figure 3. Cilia does not teach or suggest the identifying nucleotide region 1001-1040 as set forth in Table 2 for identifying Shigella dysenteriae (Claim 40) since Cilia sets forth that region as having the same sequence as the reference E. coli sequence. Cilia does not teach or suggest the identifying nucleotide C at position 92 for identifying Shigella boydii (Claim 41) since Shigella boydii is not present in the sequence alignment of Cilia. Cilia does not teach nor suggest the nucleic acid molecules having the SEQ ID NOS as set forth in Claims 42-44.

Hogan differs from Claim 37 in that Claim 37 provides an identifying nucleotide for E.coli species at an E. coli-equivalent position 88p. Hogan teaches a probe for region 995-1030. There is no teaching or suggestion in Hogan that an insertion at position 88p is identifying. Futhermore, one could not predict position 88p from the information provided in Hogan.

Hogan teaches probes for E.coli that also, to an extent of 71-76%, hybridize to Shigella dysenteriae, Shigella flexneri and to Shigella sonnei (Table 54). Therefore, Hogan teaches away from distinguishing E.coli from these three species of Shigella (Claims 38, 39 and 40) since the degree of cross-hybridization is very high.

Faruque does not teach the differentiation of species or of genus as presently claimed. Faruque does not remedy the deficiency of Cilia or Hogan in rendering the presently claimed invention obvious.

In light of the lack of any teaching or suggestion of the presently claimed invention in Cilia in view of Faruque, and of Hogan in view of Faruque, Applicants respectfully request that the rejection under 103 be withdrawn.

All matters having been addressed, reconsideration and an early indication of the allowability of Claims 37-44 is earnestly solicited.

Respectfully submitted,

Gloria L. Norberg

Date: August 4, 2000

Gloria L. Norberg
Reg. No. 36,706
Agent for Applicants

Akin, Gump, Strauss, Hauer & Feld, L.L.P.
816 Congress Avenue, Suite 1900
Austin, Texas 78701
Telephone: (512) 499-6200
Fax: (512) 703-1107